UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DLC

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/455,975	05/31/95	RUBIN J	40399/299/NI

HM12/0719

FOLEY & LARDNER
3000 K STREET N.W.
STE. 500
WASHINGTON DC 20007-5109

EXAMINER	
SAOUD,C	
ART UNIT	**PAPER NUMBER**
1646	20

DATE MAILED: 07/19/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/455,975	RUBIN et al.
Examiner	**Group Art Unit**
Christine Saoud	1646

☒ Responsive to communication(s) filed on *03 Dec 1998, 10 June 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *38-131* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *111-113* is/are allowed.

☒ Claim(s) *38-110 and 114-131* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *11*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Transitional After Final Practice

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 08 May 1998 has been entered.

Election/Restriction

2. For clarification purposes, the election/restriction history will be summarized. In paper #12, a restriction was made between claims 38-109, 114-120 and claims 110-113, directed to methods of stimulation and methods of inhibiting, respectively. In paper #14, Applicant payed the required fee under 37 CFR § 1.17(s) for the examination of an additional invention, directed to methods of inhibiting KGF activity. The original restriction was made under the premise that the inhibition methods were limited to use of an antibody (see claims 110-113). In paper #14, additional claims were added which corresponded to two additional inventions: inhibition by administration of DNA and inhibition by administration of heparin and a peptide. These inventions were restricted in paper #15, offering Applicant to pay for the examination of these additional inventions according to the transitional restriction provisions. In paper #19, Applicant additionally elected to have the method of inhibition by administration of DNA examined. Although Applicant indicated that they did not believe that any further fees were due, the fee for

examination of an additional invention was required and charged to Applicant's deposit account (see the fee under 37 CFR § 1.17(s)).

3. Therefore, claims 38-131 are pending in the instant application and under examination. Claims 12-131, in so far as they are directed to a method of inhibition by administration of heparin and a peptide, are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 19.

Specification

4. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).

(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

5. It is noted that the instant specification contains many discrepancies with regard to the arrangement of the specification. Applicant notes on page 13 of the response of paper #10 that a second substitute specification is being prepared. It would be prudent for Applicant to make sure that any substitute specification submitted in the future corrects all of the deficiencies noted in the all of the previous correspondences relating to this family of applications. For example, the Tables are part of the specification and should be incorporated into the specification at the point where they are described. The figures should be numbered according to 37 C.F.R. § 1.84 (U)(1), with the specification referring to the correct figure designations. The additional text under the figures is descriptive and should be included in the Brief Description of the Drawings and not with the figures themselves. The continuing data in the first paragraph of the specification should be updated to reflect the status of the applications referred to therein. Any and all amendments that have been submitted up to this point should be included in the substitute specification. And lastly, a marked up copy of the specification should be provided, as well as an amendment directing entry of the substitute specification and a statement that there is no new matter included. Any response to this Office action which does not include a proper substitute specification may be held to be non-responsive. This is because examination of the instant application is severely hampered by the condition of the instant application with regard to the specification. Applicant is also reminded that the claims **SHOULD NOT** be submitted as part of the substitute specification.

Claim Objections

6. Applicant should note the following typographical errors in the claims:

(1) Claim 127 includes a period before the beginning of the claim ("127. .The").

(2) Claim 126 refers to "An method".

(3) Claim 129, line 4 refers to "aid sequence o f Figure 7".

Claim Rejections - 35 USC § 112

7. Claims 38-56, 57-72, 82-101, and 114-120 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for KGF and KGF polypeptides which have an amino acid sequence as set forth in Figure 7, or is truncated within the region of amino acids 32-78, does not reasonably provide enablement for any protein that (1) has a recited molecular weight, produced by fibroblast cells and has a specific activity as recited in the claims or (2) comprises a segment of the amino acid sequence of Figure 7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification teaches a keratinocyte growth factor (KGF) of 194 amino acids in length and DNA encoding said KGF. The specification also teaches that the first 31 amino acids are a signal sequence that is cleaved in the mature protein and that amino acids 32-78 confer epithelial cell specificity to the protein. First, the language of a KGF polypeptide having a molecular weight and mitogenic activity does not give any structure to the amino acid sequence which is necessary

for this activity. The claim must recite sufficient elements necessary for enablement of the claimed invention. The instant specification discloses a single protein that is isolated from fibroblast cells that has the recited activity of the claims and there is evidence in the specification that amino acids 32-78 are ***responsible*** for conferring cell specificity to the protein. There is no reasonable expectation that any other protein isolated from fibroblast cells that has a molecular weight as recited in the claims would have the claimed activity. Therefore, it would require undue experimentation for one of ordinary skill in the art to determine which other proteins of the recited molecular weight would have the recited mitogenic activity for epithelial cells, absent evidence to the contrary.

The recitation of having a "molecular weight of between about 16 and about 30 kDa" or a "molecular weight of between about 28 and about 30 kDa" is not a sufficient structural limitation to provide the required functional limitation of having greater mitogenic activity on BALB/MK cells relative to NIH/3T3 fibroblasts. The instant specification discloses a protein which has an amino acid sequence as disclosed in Figure 7. However, the instant claims encompass any protein which has a molecular weight of between about 16 and about 30 kDa and also has an activity which is preferential for BALB/MK cells relative to NIH/3T3 fibroblasts. The structural feature of a molecular weight is not sufficient to provide the function recited in the claims. It would require undue experimentation for one of ordinary skill in the art to determine which proteins which meet the structural limitation of molecular weight would also meet the functional limitations. One of ordinary skill in the art would not believe that molecular weight alone would

confer the activity required by the claims, yet the claims do not provide any other structural characteristics. Furthermore, the instant specification provides evidence that amino acids 32-78 (see Figure 7) are ***responsible*** for conferring mitogenic specificity to the protein and therefore, would be critical or essential to the practice of the invention. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The instant specification defines KGF as including mutants and or having and at least one or more amino acid differences. (see pages 7 and 10). However, the specification is only enabling for KGF having the amino acid sequence found in Figure 7 (or specific portions as outlined above) because it does not describe the production of any KGF ***lacking*** that sequence. By following the guidance presented in the instant specification and sound scientific principles, a practitioner can **not** produce a KGF lacking the disclosed amino acid sequence and predict the functional properties of that protein.

Claims 64, 69, 88, 90, and 95 require "a sufficient number of amino acids 32-64 that said polypeptide has said greater stimulatory activity on BALB/MK cells relative to NIH/3T3 cells", however, as pointed out before, there are no number of these amino acids which will provide for this activity. This is because these amino acids alone do not provide the biological activity of stimulating BALB/MK cells. These amino acids are responsible for conferring cell specificity. If the claims were reworded such that the limitation of stimulatory activity is not associated with the 32-64 portion of the protein alone, this ground of rejection could be avoided. Additionally, a point of reference must be give for the recitation of amino acids 32-64 in that it has no meaning without indicating that these amino acids are from Figure 7.

With regard to claims 57-72 and 82-101 recite a method of stimulating by administration of KGF comprising the amino acid sequence of Figure 7 or a segment thereof. The specification teaches that amino acids 32-78 confer epithelial cell specificity to the protein. There is no support in the specification that any segment from KGF would provide the preferential mitogenic activity of a KGF polypeptide, and it would required undue experimentation to determine how the amino acids could be arranged in order to facilitate preferential mitogenic activity. Furthermore, the claim must recite sufficient elements necessary for enablement of the claimed invention. In the instant case, there is evidence in the specification that amino acids 32-78 are ***responsible*** for conferring mitogenic specificity to the protein, the specification does not teach which other portions are necessary for mitogenic activity on epithelial cells or that portions of KGF which do not include these amino acids would possess preferential mitogenic activity for epithelial cells. Therefore, it would require undue experimentation for one of ordinary skill in the art to determine which segment of KGF would confer preferential mitogenic activity for epithelial cells if it did not include that portion responsible for the cell specificity necessary for facilitating the activity recited in the claim, absent evidence to the contrary.

8. Claims 49-56, 82-110, and 121-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide enablement for the invention which is commensurate in scope with claims to "accelerating or improving the healing of a wound" in a patient (claims 49-56, 82-109), "a method of inhibiting keratinocyte growth factor (KGF) activity *in vivo*" (claim 110), or "treating a patient having an epithelial skin condition" (claims 121-131). The specification provides a protein, keratinocyte growth factor (KGF), which stimulates epithelial cells specifically (i.e. does not stimulate fibroblast cells). The specification is also enabled for using this protein (and/or pharmaceutical compositions) for stimulating epithelial cell growth, either *in vivo* or *in vitro*. However, the specification fails to enable a method for treating a patient for any particular condition by stimulation or inhibition of KGF because there is no disclosure of such a method which would provide for the benefits of the instant claims. The claims must recite sufficient elements and steps for achieving the claimed method; without knowing what amount to administer and for what length of time, one of ordinary skill in the art would not be able to practice the invention as claimed. (See *In re Colianni* (CCPA) 195 USPQ 150.) The issue of skill in the art and enablement was addressed in the recent decision Genentech, Inc. v. Novo Nordisk, 42 USPQ2d 100 (CAFC 1991). In this case, the Board held that "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966)). Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of

the public to understand and carry out the invention. ....It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." The knowledge gained from the specification that KGF stimulates epithelial cells is not sufficient for a claim to accelerating or improving the healing of a wound because such a method is not provided for in the instant specification. Likewise, the fact that KGF can be inhibited in vitro does not provide for a method of treating a patient having an epithelial skin condition by inhibition of KGF. There is no evidence to support the conclusion that all epithelial skin conditions are caused by an over-expression of KGF, and therefore, could be treated by inhibition of KGF. There are no examples in the instant specification that inhibition of KGF will provide a therapeutic treatment for any known condition of the skin. Lastly, there is no specific method disclosed that would enable an artisan to practice the method as claimed. Therefore, the specification is not enabled for the claimed method, absent evidence to the contrary.

It should also be noted that claims 121 and 126 are generic to any compound which inhibits KGF. This is similar to a single means claim in that the specification only discloses a limited number of compounds which have this activity. MPEP 2164.08(a) defines a single means claim as a claim which covered every conceivable means for achieving the stated purpose when the specification disclosed at most only those means known to the inventor. This type of claim was held to be nonenabling for the scope of the claim in In re Hyatt , 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983) because the specification disclosed at most only those means known to the

inventor. When claims depend on a recited property, a fact situation comparable to Hyatt is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. This appears to be the instant case and the claim is not commensurate in scope with the specification.

With regard to claims 110 and 121-128 and the use of antibodies, the specification describes the neutralizing antibodies to KGF (page 31-32), monoclonal mouse antibodies (page 56), and polyclonal rabbit antibodies (page 56). The specification does not provide any examples or strategies for a method of treating conditions that require specific inhibition of epithelial cells comprising administration of an antibody. There is insufficient information or nexus with respect to the ability of KGF antibodies (monoclonal, polyclonal, or neutralizing) to inhibit epithelial cells for treating conditions. Pharmaceutical therapies (especially utilizing antibodies) are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein by be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown; may make the protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment.

In vitro and animal model studies involving growth factors have not correlated well with *in vivo* clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs

can be species- and model-dependent, it is not clear that reliance on *in vitro* binding and functional inhibition studies accurately reflects the relative efficacy of the claimed therapeutic method. The specification describes several types of antibodies (neutralizing, monoclonal, polyclonal, murine, rabbit), but the specification is deficient in teaching which, if any, of these antibodies is effective in specifically inhibiting epithelial cells. The claimed method encompasses the use of an antibody (any antibody) against KGF to specifically inhibit epithelial cells, however, other factors (especially aFGF) also stimulate epithelial cells (see Table I-1). It has not been established that the inhibition of a single growth factor would be effective for inhibiting epithelial cells and a person of ordinary skill in the art would not reasonable expect that the mere inhibition of KGF would result in inhibition of epithelial cells. With regard specifically to the enablement of the use of an antibody therapeutically, Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for *in vivo* human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3) (Tibtech, 1993). Humanized antibodies may still present serious problems with immunogenicity, since the idotype of such antibodies will contain unique amino acid sequences.

The specification does not provide sufficient information or nexus *a priori* that establishes the efficacy of the instant method for the treatment of a condition. In the absence of evidence commensurate in scope with the claims, it appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification

alone. The specification does not adequately teach how to effectively treat any disease or condition or reach any therapeutic endpoint in humans by administering antibodies to KGF. The specification does not teach how to extrapolate data obtained from in vitro binding inhibition assays to the development of effective in vivo therapeutic methods, commensurate in scope with the claimed method. Furthermore, the specification does not even provide examples of in vitro binding inhibition assays. Therefore, it is not clear that the skilled artisan could predict the efficacy of the claimed method for treating conditions requiring specific inhibition of epithelial cells, encompassed by the claims.

With regard to claims 121-131 as directed to methods of inhibition by administration of a DNA probe, the instant specification fails to provide any useful information which would enable one of ordinary skill in the art to practice such a method. The art of gene therapy and anti-sense therapy is very unpredictable at the present time, and even more so at the time of the instant invention. Without specifics of the method to be used (including probe length, composition, administration amounts, dosing schedules, etc.), the skilled artisan would not be able to practice the claimed method, absent evidence to the contrary.

9. Claims 39, 41-42, 58, 60-61, 83, 85-86, 115, and 117-118 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims refer to DNA molecules which encode a polypeptide which stimulates BALB/MK cells to a greater degree compared to NIH/3T3 cells. However, the specification only provides for a polypeptide which stimulates BALB/MK cells 50 times greater than NIH/3T3 cells, rather than the varying degrees which are now recited in the claims. The instant specification does not provide for these new limitations of stimulation, nor does it provide for KGF polypeptides that differ in their ability to stimulate BALB/MK cells. A single KGF polypeptide is provided and it has the amino acid sequence as depicted in Figure 7, absent evidence to the contrary. Therefore, the claims are directed to subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, absent evidence to the contrary.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 38-110 and 114-120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Any claim which is not specifically recited below is indefinite for depending on an indefinite claim because the further limitations of the dependent claims do not correct the deficits indicated below.

In claims 38, 57, 110, the use of "*in vivo*" along with the recitation of "administering to a patient" is redundant and confusing. The recitation that the administration is to be to a patient necessarily dictates that the method must be an in vivo method. Therefore, the inclusion of "*in vivo*" is confusing because it is not clear that there is an in vitro method that comprises administration to a patient. The claims could be clarified by the removal of the phrase "*in vivo*".

Claims 38, 48, 49, 56, 114, and 120 refer to a molecular weight without any recitation of how the molecular weight was determined. Without a recitation of the method of calculating the molecular weight (i.e. as calculated by SDS Page under reducing conditions), the claims are unclear and indefinite because molecular weight can vary significantly depending on the conditions which are used. Therefore, without a recitation of the method which results in the recited molecular weight, the claims are indefinite because the metes and bounds cannot be determined.

Claims 57 and 82 are indefinite because it is not clear what the "thereof" refers to; either the polypeptide or the sequence. Therefore, it is not clear what the metes and bounds of "segment" are in the claim.

Allowable Subject Matter

12. Claims 73-81 have been rejected as being indefinite because they depend from claims that are indefinite. However, if these claims were written in independent form directed to a method of stimulating epithelial cells comprising administering to a patient the polypeptides of these claims, these claims would appear to be allowable.

13. Claims 111-113 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 3PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

July 16, 1999

CHRISTINE SAOUD
PATENT EXAMINER

Christine Saoud